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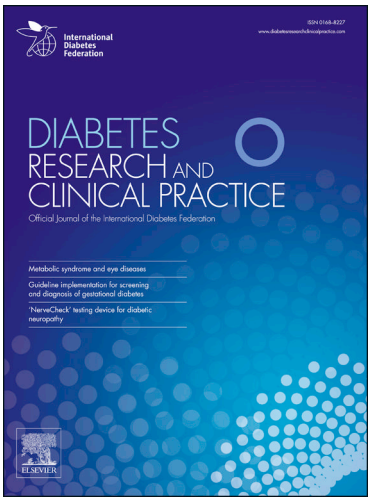

Diabetes-Attributable Mortality in the United States from 2003-2016 Using a Multiple-Cause-of-Death Approach

Fatima Rodriguez, Manuel R. Blum, Titilola Falasinnu, Katherine G. Hastings, Jiaqi Hu, Mark R. Cullen, Latha P. Palaniappan

PII: S0168-8227(18)31657-7
DOI: https://doi.org/10.1016/j.diabres.2019.01.015
Reference: DIAB 7593

To appear in: *Diabetes Research and Clinical Practice*

Received Date: 1 November 2018
Revised Date: 18 December 2018
Accepted Date: 9 January 2019

Please cite this article as: F. Rodriguez, M.R. Blum, T. Falasinnu, K.G. Hastings, J. Hu, M.R. Cullen, L.P. Palaniappan, Diabetes-Attributable Mortality in the United States from 2003-2016 Using a Multiple-Cause-of-Death Approach, *Diabetes Research and Clinical Practice* (2019), doi: https://doi.org/10.1016/j.diabres.2019.01.015

Title: Diabetes-Attributable Mortality in the United States from 2003-2016 Using a Multiple-Cause-of-Death Approach

Short Title: Contemporary Diabetes Mortality Patterns

Authors: Fatima Rodriguez, MD, MPH[1*], Manuel R. Blum, MD[1,2*], Titilola Falasinnu, PhD,[3] Katherine G. Hastings, MPH[4], Jiaqi Hu, MPH[4], Mark R. Cullen, MD[4], Latha P. Palaniappan, MD, MS[4]

* These authors contributed equally.

Author Affiliations: [1] Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA; [2]Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland; [3]Department of Health Research and Policy, Stanford School of Medicine, Stanford, CA; [4]Division of Primary Care and Population Health, Stanford University School of Medicine, Stanford, CA.

Corresponding Author:
Fatima Rodriguez, MD, MPH
Division of Cardiovascular Medicine, Stanford University
870 Quarry Road, Falk CVRC
Stanford, CA 94305-5406
Tel: 650-723-6661
Fax: 650-725-1599
e-mail: frodrigu@stanford.edu

Word Count: 2720

ABSTRACT

Aims: Deaths attributable to diabetes may be underestimated using an underlying cause of death (COD) approach in U.S. death records. This study sought to characterize the burden of diabetes deaths using a multiple-cause of death approach and to identify temporal changes in co-reported causes of death among those with diabetes listed anywhere on their death records.

Methods: COD were identified using data from the National Center for Health Statistics from 2003-2016. We calculated age-adjusted mortality rates for diabetes as the underlying or contributing COD by race/ethnicity. We used ICD-10 codes to identify leading causes of death among those with and without diabetes on their death records. We compared temporal changes in deaths due to cardiovascular disease, cerebrovascular disease, cancer, and other causes.

Results: The study population included 34,313,964 decedents aged ≥25 from 2003-2016. Diabetes was listed as an underlying COD in approximately 3.0% (n=1,031,000) and 6.7% (n=2,295,510) of the death records, respectively. Decedents with diabetes listed as an underlying COD experienced a 16% decline in mortality, and the race/ethnicity-specific average annual percentage changes (AAPC) showed significant declining trends for most groups (AAPC ranged from 0.18 to -2.83%). Cardiovascular disease remained the leading underlying COD among diabetes-attributable deaths, although its proportion of deaths fell from 31 to 27% over time. Co-reported COD diversified, and were more likely to include hypertension and hypertensive renal disease among those with diabetes on their death records.

Conclusions: Our findings underscore the importance of using a multiple-cause-of-death approach for more completely characterizing diabetes' contribution to mortality.

Key words: diabetes; death records; epidemiology; disparities

RESEARCH IN CONTEXT

Evidence before this study

Previous studies reported that diabetes is underestimated as a cause of death on death records. U.S. mortality records indicate both the "underlying cause of death," defined as the disease or injury that initiated the train of events leading directly to death and up to 20 "contributing causes of death." Although the prevalence of diabetes in the adult US population continues to increase, outcomes in this population are improving, including cardiovascular mortality.

Added value of this study

Using over a decade of contemporary national U.S. mortality data, we characterized the burden of diabetes using a multiple-cause-of-death analysis and showed that mortality rates are declining for those with diabetes on their death records. We also uncovered differences in diabetes reporting on death records by race/ethnicity, and showed that declining mortality trends apply to most, but not all race/ethnic groups. We showed that contributing causes of death diversified as cardiovascular mortality declined in diabetes-attributable deaths.

Implications of all the available evidence

Examining diabetes as an underlying cause of death results in significant underrepresentation of diabetes-attributable mortality. A multiple-cause of death analysis that includes both underlying and contributing causes of death better depicts the true contribution of diabetes to U.S. mortality. With the diversification of contributing causes of death in diabetes-attributable deaths, a focus on broader disease prevention strategies among individuals with diabetes – beyond cardiovascular disease – is warranted.

BACKGROUND

Affecting almost 10% of the U.S. population, diabetes mellitus (DM) is a common chronic condition associated with significant premature morbidity and mortality.[1-3] DM has consistently been listed as one of the top causes of death among Americans, and is projected to become the seventh leading cause of death worldwide by 2030.[4] Despite this burden, studies have shown that DM has been underestimated as a cause of death on death certificates for decades.[5,6] The Centers for Disease Control and Prevention indicated that only 35-40% of decedents with clinically diagnosed DM actually had DM listed on their death certificate, and that only 10-15% of these decedents had DM listed as the underlying cause of death.[7]

U.S. mortality records report both the "underlying cause of death," defined as the disease or injury that initiated the train of events leading directly to death and up to 20 "contributing causes of death."[8] Because DM is less likely to be a primary cause of death and more frequently contributes as a risk factor for cardiovascular and other leading causes of death, considering the burden of DM using multiple-cause-of-death analyses has been recommended by prior literature.[9,10] Using this type of approach may present a more complete picture of DM as a cause of death. In fact, other studies using a multiple-cause-of-death approach in various domestic and international settings have documented that DM is more than twice as likely to be listed as contributing than underlying cause of death.[9-18] Furthermore, there are temporal differences in DM reporting as an underlying versus contributing cause of death.[19] Our study extends prior work by considering a decade of contemporary death record data and examining these reporting patterns by race/ethnicity.

Although the prevalence of diabetes continues to increase, paralleling the obesity epidemic, outcomes among individuals with diabetes have been improving.[20] Even among individuals with diabetes, declining rates of cardiovascular disease deaths highlight the need to focus on broader disease prevention strategies.[21] Individuals with diabetes are now increasingly dying from other common causes of death such as cancer, renal disease, infections, and unintentional harm. Thus, using national mortality records from 2003-2016, our study had two primary objectives: 1) to quantify recent mortality trends attributable to DM on the death records using underlying and contributing cause of death approaches; 2) to identify potential changes over time in co-reported causes of death among those with DM listed anywhere on their death records.

METHODS

Study Population

We examined U.S. mortality records from the National Center for Health Statistics (NCHS) Multiple Cause of Death mortality files from 2003–2016 for decedents in the 50 states and the District of Columbia. Year of death, sex, age at the time of death, sex, race/ethnicity, and educational attainment (less than high school, high school education, or more than high school education) were identified from NCHS. Race/ethnicity was recorded on death certificates by the funeral director using state guidelines and coded to the five NCHS categories of interest (i.e., Asian American/Pacific Islanders (herein Asian), non-Hispanic Black, Hispanic/Latinos (herein Hispanic), non-Hispanic White (NHW), and American Indian/Alaskan Native. Underlying cause of death was defined as the disease or injury that initiated the events resulting in death using the International Classification of Diseases, 10th revision (ICD-10) coding scheme.[8] Contributing causes of death included any other causes of death mentioned in the death certificates (up to 20),

not including the underlying cause of death. A death record with an ICD-10 code E10-14 was considered to represent a diabetes-attributable death (multiple-cause-of-death approach), either as underlying cause of death or as contributing cause of death. Death records without one of the aforementioned ICD-10 codes were considered to represent non-diabetes-attributable deaths. Only US residents who were 25 years or older at the time of death were included in the analysis due to small sample sizes in the younger age categories and to potentially exclude any cases of infant mortality.

Cause of Death Definitions

Underlying causes of death were classified into four general categories based on ICD-10 guidelines: cardiovascular (ICD-10 codes I00-09, I11, I13-59, I70-99), cerebrovascular (ICD codes I60-69), cancer (ICD codes C00-97), and other causes. The other causes of death of special interest among those with diabetes listed anywhere on the death certificate were defined according to the following categories: 1) Infectious disease (ICD codes J00-22, A00-99, B00-99), 2)Chronic respiratory disease (ICD codes J40-47), 3) Chronic liver disease (ICD codes K70, K73-74), 4) Hypertension or Hypertensive chronic kidney disease (ICD codes I10, I12), 5) Alzheimer disease (ICD code G30), 6) Accidents (ICD codes V01-99, W00-99, X01-59, Y85-86), 7) Self-harm (ICD codes X60-84, X87.0, U03), 8) Acute or chronic kidney disease (N17-19).

Statistical Analysis

Age-adjusted mortality rates (AMRs) were calculated for DM as an underlying and contributing cause of death. For temporal trends, these were standardized to the 2000 U.S. Census population

by age (5-year age categories). The population estimates by age category, sex and race/ethnicity were retrieved from the CDC WONDER database for the years 2003 to 2016.[22] Demographic characteristics and frequencies/percentages of the number of causes of deaths were described for decedents with diabetes as the underlying cause of death, diabetes as either underlying or contributing cause of death and non-diabetes deaths. Between-group comparisons were made using two-sided t-tests for continuous variables and chi-squared tests for categorical variables. To quantify trends over time, average annual percent changes were calculated for each race/ethnic group separately using Joinpoint regression software with a grid search method and a maximum of two joinpoints, assuming uncorrelated errors (sensitivity analyses with fitting autocorrelated errors models with correlations of 0.1 to 0.3 were performed to assess the robustness of this assumption [results not shown]).[23]

Data management and analyses were performed in Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC), R (version 3.5), and Joinpoint Regression Program (version 4.6.0.0 - April 2018; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute). Statistical tests were based on 2-sided tests with a significance level of 0.05.

RESULTS

A total of 34,313,964 decedents over the age of 25 during 2003-2016 were included in our analysis. Table 1 shows the characteristics of decedents who had diabetes listed as an underlying cause of death, contributing cause of death or anywhere on their death certificate as compared with decedents without mention of DM on their death certificates. DM was listed as an underlying and contributing cause of death in approximately 3.0 (n=1,031,000) and 6.7%

(n=2,295,510) of the death records, respectively. Those with DM on their death certificate were younger at the time of death, more likely to be non-white, and have lower educational attainment levels ($p<0.001$ for all comparisons). Those with DM on their death certificates were more likely to have more causes of death listed on their death certificates as compared with those without DM listed on the death certificate (4.4 vs. 2.7, $p<0.001$).

The overall adjusted mortality rates declined overtime for all groups (Table 1). The adjusted mortality rates for diabetes as an underlying cause of death declined by 16% since 2003. A similar pattern was seen for DM as a contributing cause of death (adjusted mortality rate declined by 11%) and for DM listed anywhere on the death certificate (adjusted mortality rate declined by 13%). Figure 1 shows the overall decline in age-adjusted mortality deaths for diabetes listed as an underlying cause of death. Death records were on average 2.23 (95% confidence interval 2.18-2.28) times more likely to report diabetes as a contributing cause of death than an underlying cause of death.

DM-attributable deaths decreased among all racial/ethnic groups, although there were differences in DM reporting on the death records by race/ethnicity (Figure 2). Non-Hispanic Blacks were more likely to have DM as both an underlying and contributing cause of death as compared with all other racial/ethnic groups, whereas NHWs and Asians were least likely to have DM listed anywhere on their death records. Except for the group of Alaskan Natives/American Indians, the race/ethnic specific average annual percent changes showed statistically significant declining trends both for DM as an underlying and contributing cause of death (Table 3).

Cardiovascular disease has remained the leading cause of death among those with DM listed as underlying or contributing cause of death on their death certificates (Figure 3). However, cardiovascular and cerebrovascular disease as underlying cause of death are decreasing for both the general population and for those with DM listed as a contributing cause of death on their death records. In 2002, cardiovascular diseases accounted for 45% of the underlying causes of death among those with DM listed as contributing cause of death as compared to 39% in 2016. Cancer deaths account for an overall smaller proportion of underlying causes of deaths among those with DM as a contributing cause of death versus thus without DM.

Table 2 shows the distribution of the leading underlying causes of death among those with DM listed as an underlying or contributing cause of death versus those without DM mentioned on their death certificates for the years 2003 and 2016. Overall, decedents with DM listed on their death certificate were more likely to have cardiovascular disease listed on their death certificates and less likely to have cancer listed anywhere on their death records. Hypertension and hypertensive renal diseases accounted for a greater proportion of deaths among dose with DM on their death certificates. In 2016, 14 and 11% of those with diabetes as an underlying or contributing cause of death on their death records, respectively, also had hypertension/hypertensive renal disease listed. Compared with 2003, the "Other" non-leading causes of death occurred more frequently in 2016 in all groups (32 vs 23% in those with diabetes listed as an underlying cause of death, and 34 vs 26% in those with diabetes listed as a contributing cause of death).

DISCUSSION

Using national death records, we identified contemporary trends in mortality for those with diabetes listed on the death certificate compared to those without diabetes listed. Overall, deaths have decreased similarly for both groups (with and without diabetes on death certificates) over the study period (2003-2016). We also documented changing patterns in the etiology of underlying cause of death among those with DM listed on their death certificates. We found that by using only an underlying cause of death, DM-attributable causes of deaths may be significantly undercounted. Although disparities in DM-attributable deaths were noted by race/ethnicity, all groups except Alaskan Natives/American Indians experienced an overall decline in DM-attributable deaths as measured by both underlying and contributing of death. Over the last 13 years, there has been a steady decline in total mortality, particularly cardiovascular disease mortality among patients with DM listed on their death records. Given the decrease in competing causes of death, there is an increasing proportion of deaths attributable to other etiologies such as hypertension and hypertensive renal disease.

We found that only 3% of death records reported DM as an underlying cause of death. When considering DM as anywhere on the death records (a multiple-cause-of-death approach), this rose to 9.7%, more closely paralleling the estimated population prevalence of DM.[24] These results extend prior work that has shown that DM is underestimated as an underlying cause of death in the U.S. death records.[9,11-17] Similar to our findings, using a multiple-cause-of-death approach increases the documented prevalence of DM in international death certificates by 2 to 4-fold.[10,18] Other results from the Translating Research into Action for Diabetes (TRIAD) Study found an increasing trend of recording diabetes as an underlying cause of death from 2000-2007,

but not for the recording of diabetes anywhere on the death certificate.[19] Our findings underscore that considering only a single underlying cause of death may obfuscate important contributions from multisystem chronic diseases like DM to mortality.

Our results are concordant with recently published report showing the declining rates of vascular disease among individuals with diabetes.[21] Using data from the National Health Interview Survey Linked Mortality files, the investigators found that from 1988 to 2015, all-cause mortality declined among individuals with diabetes. The proportion of deaths from vascular causes declined whereas the proportion of non-cancer, non-vascular deaths increased among individuals with diabetes. Similar to our study, this data showed that the proportion of death from cancer among individuals with diabetes did not significantly increase over time.

Our study also uncovered differences in DM reporting on death records by race/ethnicity. Blacks, Alaskan Indian/Native Americans, and Hispanics were more likely to have DM listed as an underlying and contributing cause of death as compared to NHWs. This is likely explained to a higher prevalence of diabetes in racial/ethnic minority groups in the U.S. All race/ethnic groups except Alaskan Indians/Native Americans experienced a decline in DM-attributable deaths during the study period. This trend likely may be attributed to the high prevalence of diabetes and its complications among Alaskan Indians/Native Americans.[25,26] Prevention programs targeting this small but significant portion of the U.S. population are needed to ensure that all groups may benefit from the overall observed reduction in DM-related deaths.

Similar to other studies, our results show favorable changes in mortality among patients with DM listed on their death records.[20,27] Overall death rates are declining among those with DM listed on their death records and the causes of death are increasingly diverse. This likely reflects significant strides in preventive health measures among individuals with diabetes and others. The reduction in CVD deaths may also be explained by overall improvement in the treatment of myocardial infarctions as well as primary and secondary CVD prevention efforts among individuals with diabetes.[28] Although DM is associated with an increased risk of a wide range of CVD, the risks have been shown to vary by CVD subtype.[29] Increasingly, as novel diabetes drugs continue to improve cardiovascular outcomes, we expect the positive reductions in CVD mortality among individuals with diabetes to continue.[30]

DM is a multisystem disease and, as DM-related vascular complications continue to decline, a rise in other causes of death is expected. For example, we found that those with DM on their death record as three times as likely to have hypertension and renal disease co-reported on their death records. These findings have important clinical and public health interventions to reduce DM-related morbidity. In addition to improving glycemic control among individuals with diabetes, interventions seeking to aggressively control hypertension and diabetic nephropathy may provide significant gains in diabetic mortality.

Our results should be interpreted in the light of several limitations. First, death records are prone to reporting errors which may have impacted our findings. Studies have shown that nearly one-third of all death certificates may be erroneously completed, particularly for diabetes. [5,6,31-33] The misattribution of DM in death certificates may be due to a variety of problems such as

inaccuracies at several steps in the certification process,[34] missing information[35], and poor accuracy in resident-physician completion of death certificates. DM may be particularly prone to inaccurate reporting on death records due to the medical subjectivity and interpretation of identifying diabetes as a contribution to death.[16,17,36] Our study does not account for the true DM prevalence on the population but instead uses a multiple-cause-of-death approach to determine the burden of DM on overall mortality and cause-specific mortality as measured by the death records.

CONCLUSION

In summary, using contemporary national mortality records, we document significant underrepresentation of diabetes on mortality, especially when examining diabetes as an underlying cause of death. A multiple-cause-of-death analysis that includes both underlying and contributing causes of death better depicts the true contribution of diabetes in U.S. mortality. Those with DM listed on their death certificates have experienced an overall decline in death rates and other co-reported causes of death have diversified.

FUNDING SOURCES

Dr. Rodriguez was supported by the McCormick Galiban Faculty Fellowship from Stanford University. Dr. Blum was funded by a grant from the Swiss National Science Foundation (P2BEP3_175289). Dr. Falasinnu was funded by a Diversity Supplement for NHLBI from the CASPER grant (1R01HL126172-01A1).

DECLARATION OF INTERESTS

The authors have no disclosures to report.

AUTHOR CONTRIBUTIONS

FR and LP contributed to the study conception and design. MB, TF, and JH analyzed and interpreted the data. KH and MC contributed to data interpretation. All authors contributed to the drafting of the manuscript, provided critical revisions, approved the final version, and are agreeable to being accountable for all aspects of the work.

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Table 1. Characteristics of the Descendants by Diabetes Reporting Status from 2003-2016 (n=34,313,964)

	Diabetes as Underlying Cause	Diabetes as Contributing Cause	Diabetes Multiple Cause of Death	Non-Diabetes Deaths	All deaths
N (2003-2016)	1,031,000	2,295,510	3,326,510	30,987,454	34,313,964
Female (n, %)	503,377 (49)	1,106,799 (48)	1,610,176 (48)	1,5704,807 (51)	17,314,983 (50)
Age (mean, SD)	72.5 (14.1)	74.6 (12.9)	73.9 (13.3)	74.5 (16.0)	74.5 (15.8)
Race/ethnicity (n, %)					
NH White	715,956 (69)	1,705,388 (74)	2,421,344 (73)	25,213,988 (81)	27,635,332 (81)
NH Black	178,723 (17)	324,098 (14)	502,821 (15)	3,389,848 (11)	3,892,669 (11)
Asian/PI	27,119 (3)	61,675 (3)	88,794 (3)	601,157 (5)	689,951 (2)
Hispanic	97,284 (9)	185,667 (8)	282,951 (9)	1,617,401 (5)	1,900,352 (6)
Alaskan Native/American Indian	11,918 (1)	18,682 (1)	30,600 (1)	165,060 (1)	195,660 (1)
Education (n, %)					
< High school	293,898 (30)	646,844 (29)	940,742 (29)	7,511,341 (25)	8,452,083 (26)
High school	420,349 (42)	937,674 (42)	1,358,023 (42)	12,822,772 (43)	14,180,795 (43)
> High school	280,809 (28)	629,148 (28)	909,957 (28)	9,490,113 (32)	10,400,070 (31)
Average number of COD (mean, SD)	3.8 (1.6)	4.7 (1.8)	4.4 (1.8)	2.7 (1.6)	2.9 (1.7)
Number of COD (n, %)					
1	38903 (4)	1 (0)	38904 (1)	8193357 (26)	8232261 (24)
2	152632 (15)	170881 (7)	323513 (10)	8238840 (27)	8562353 (25)
3	300138 (29)	449339 (20)	749477 (23)	6510455 (21)	7259932 (21)
4	263015 (26)	568465 (25)	831480 (25)	4038872 (13)	4870352 (14)
5	140907 (14)	468712 (20)	609619 (18)	2103400 (7)	2713019 (8)
6	71945 (7)	303537 (13)	375482 (11)	1025049 (3)	1400531 (4)
7	34588 (3)	169406 (7)	203994 (6)	478841 (2)	682835 (2)
≥8	28872 (3)	165169 (7)	194041 (6)	398640 (1)	592681 (2)
Adjusted mortality rate (n per 100,000; 95% CI)					
2003-2005	37.7 (37.6 - 37.9)	79.1 (78.9 - 79.3)	116.8 (116.5 - 117.1)	1097.3 (1096.5 - 1098.2)	1214.1 (1213.2 - 1215.0)
2006-2010	32.8 (32.7 - 33.0)	76.0 (75.8 - 76.2)	108.8 (108.6 - 109.0)	1022.1 (1021.5 - 1022.7)	1130.9 (1130.3 - 1131.6)
2011-2016	31.3 (31.3 - 31.4)	70.5 (70.3 - 70.6)	101.8 (101.6 - 102.0)	989.4 (988.9 - 990.0)	1091.2 (1090.7 - 1091.8)

Abbreviations: CI, confidence interval; COD, cause of death; n, number; NH, non-hispanic; PI, Pacific Islander; SD, standard deviation

For all comparisons of "Multiple Cause of Death" vs. "Non-Diabetes deaths", p-value <0.0001. Adjusted mortality rate was adjusted to US Census 2000 population by age.

Table 2. Co-reported Causes of Death by Diabetes Reporting Status in Death Records, 2003 and 2016

Description	ICD10 codes	N (%)		
YEAR 2003		**Diabetes = underlying**	**Diabetes = contributing**	**No diabetes**
Cardiovascular disease	I00-09, I11, I13-I59, I70-99	79493 (41)	192087 (37)	1647121 (30)
Cancer	C00-97	2424 (1)	33125 (6)	665282 (12)
Infectious disease	J00-22, A00-99, B00-99	10618 (5)	29304 (6)	376278 (7)
Chronic respiratory disease	J40-47	3386 (2)	21481 (4)	235199 (4)
Cerebrovascular disease	I60-69	10551 (5)	24971 (5)	241285 (4)
Hypertension/Hypertensive renal disease	I10, I12	20146 (10)	46537 (9)	186087 (3)
Accident	V01-99, W00-99, X01-59, Y85-86	800 (0)	5009 (1)	119651 (2)
Chronic liver disease	K70, K73-74	603 (0)	3419 (1)	39918 (1)
Acute or chronic kidney disease	N17-19	20649 (11)	26819 (5)	168517 (3)
Intentional self-harm	X60-84, X87.0, U03	3 (0)	156 (0)	27663 (0)
Alzheimer dementia	G30	1181 (1)	5711 (1)	92569 (2)
Other	-	45089 (23)	133916 (26)	1754474 (32)
Total number of COD		**194943**	**522535**	**5554044**
YEAR 2016		**Diabetes = underlying**	**Diabetes = contributing**	**No diabetes**
Cardiovascular disease	I00-09, I11, I13-I59, I70-99	85963 (39)	222120 (32)	1662058 (24)
Cancer	C00-97	2622 (1)	43891 (6)	750642 (11)
Infectious disease	J00-22, A00-99, B00-99	9115 (4)	30578 (4)	387633 (6)
Chronic respiratory disease	J40-47	5243 (2)	33265 (5)	274983 (4)
Cerebrovascular disease	I60-69	8173 (4)	23192 (3)	216241 (3)
Hypertension/Hypertensive renal disease	I10, I12	31300 (14)	74887 (11)	262113 (4)
Accident	V01-99, W00-99, X01-59, Y85-86	860 (0)	8799 (1)	179871 (3)
Chronic liver disease	K70, K73-74	1008 (0)	5721 (1)	64275 (1)
Acute or chronic kidney disease	N17-19	4346 (2)	6512 (1)	188497 (3)

Intentional self-harm	X60-84, X87.0, U03	2 (0)	228 (0)	40181 (1)
Alzheimer dementia	G30	1012 (0)	9013 (1)	132198 (2)
Other	-	70601 (32)	238599 (34)	2692289 (39)
Total number of COD		**220245**	**696805**	**6850981**

COD = causes of death

Table 3. Annual Percent Change in Diabetes Mortality By Race/Ethnicity, 2003-2016

Race/Ethnicity	Diabetes as an Underlying Cause of Death		Diabetes as a Contributing Cause of Death	
	AAPC (95% CI)	p-value	AAPC (95% CI)	p-value
NH White	-1.56 (-2.03 to -1.08)	<0.001	-0.95 (-1.11 to -0.78)	<0.001
NH Black	-2.24 (-2.68 to -1.80)	<0.001	-2.06 (-2.66 to -1.46)	<0.001
Asian/PI	-0.91 (-1.34 to -0.48)	<0.001	-2.17 (-2.43 to -1.92)	<0.001
Hispanic	-2.83 (-3.52 to -2.14)	<0.001	-1.79 (-2.04 to -1.55)	<0.001
Alaskan Native/American Indian	-0.80 (-1.99 to 0.40)	0.19	0.18 (-0.26 to 0.62)	0.39

Abbreviation: AAPC, average annual percent change; CI, confidence interval; NH, non-Hispanic

FIGURE 1 . Age-Adjusted Mortality (per 100,000) by Diabetes as an Underlying versus Contributing Causes of Death, 2003-2016

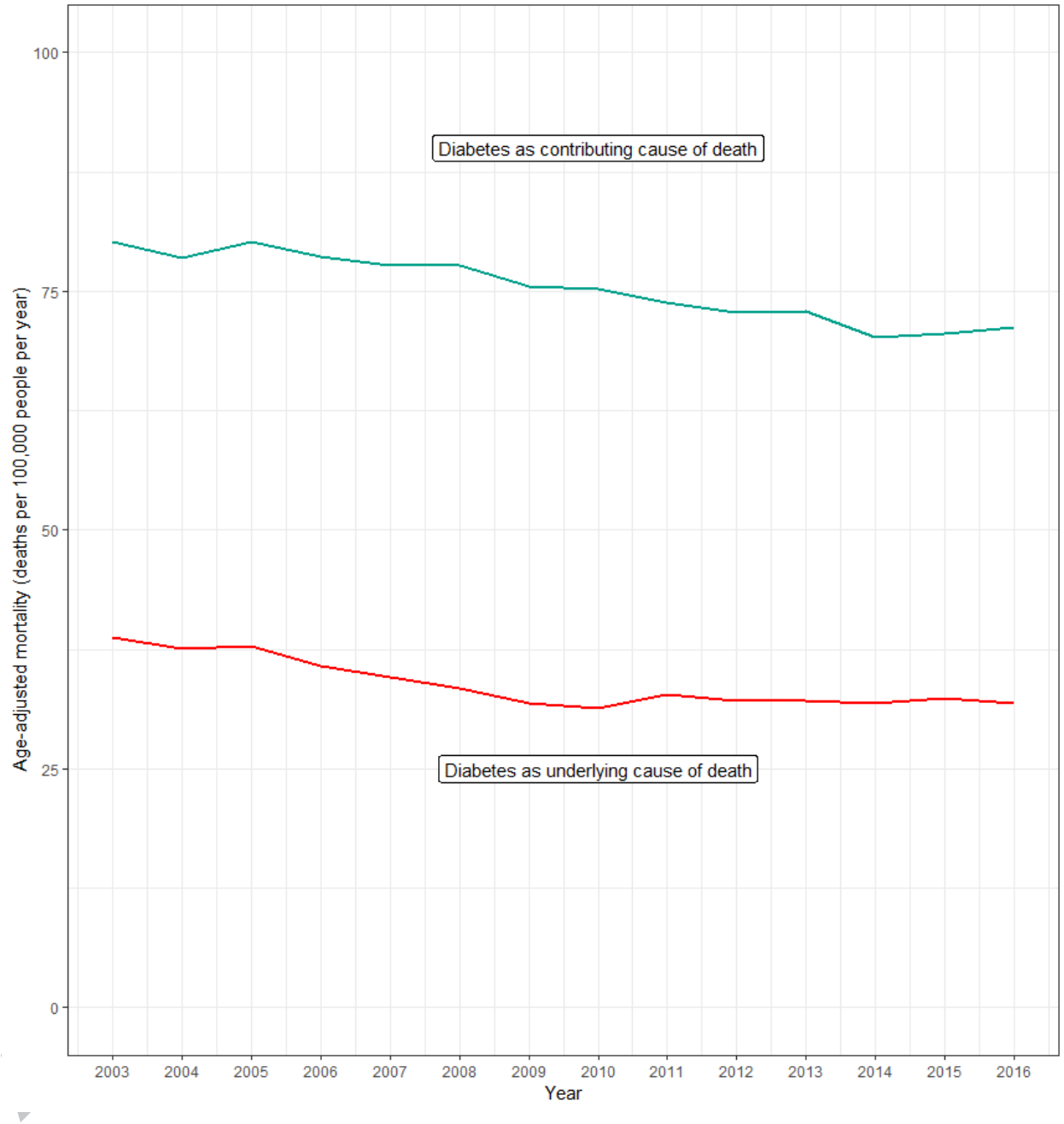

FIGURE 2. Age-Adjusted Changes in Diabetes Mortality by Race/Ethnicity, 2003-3016

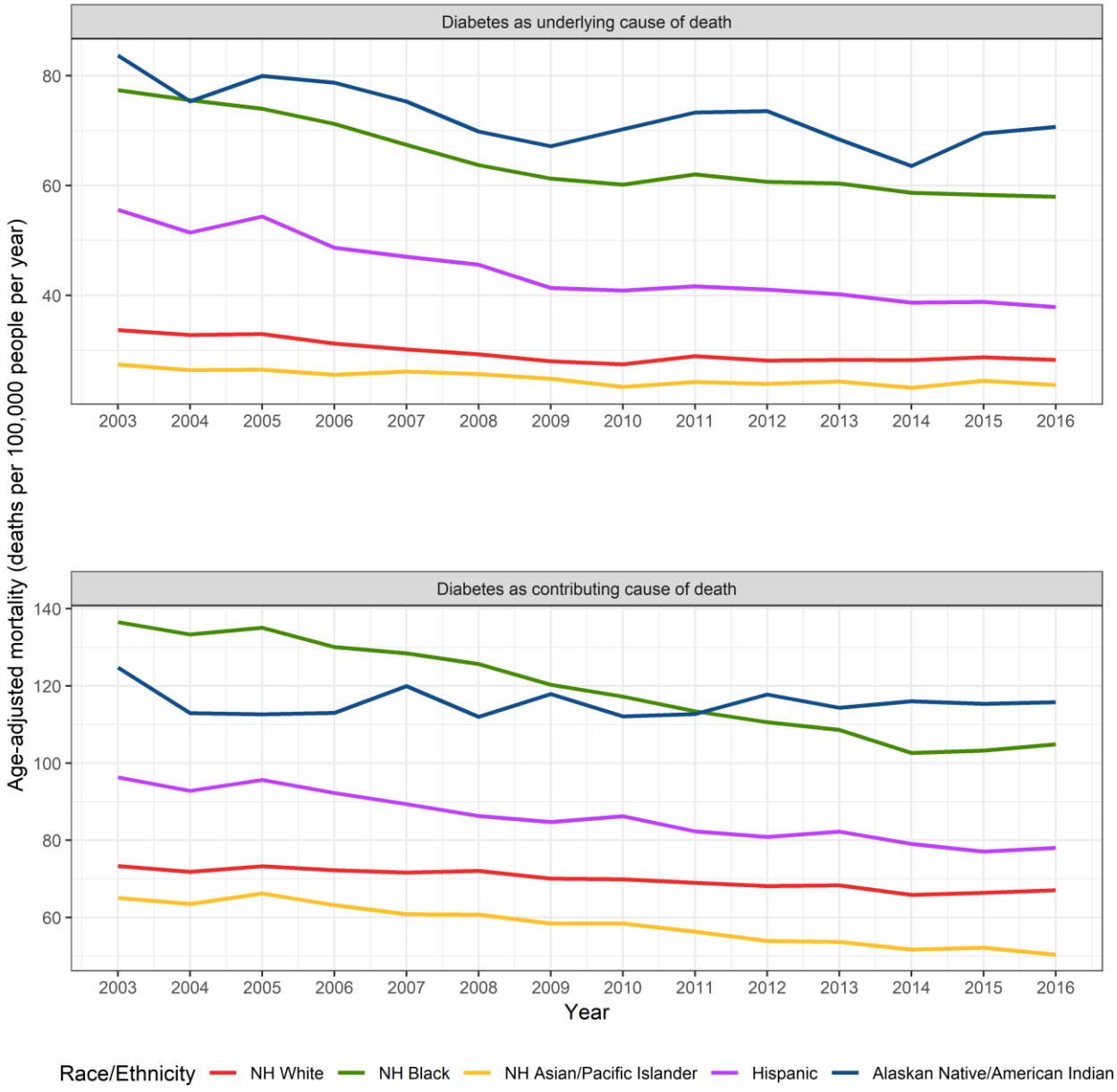

FIGURE 3. Underlying Causes of Death due to Cardiovascular Disease, Cerebrovascular Disease, and Other Causes by Diabetes Status